

Scientific Abstract

We have developed a non-viral tumor-targeted systemic gene transfer delivery complex for use against cancer. This complex is composed of a plasmid vector carrying the normal human p53 tumor suppressor gene, encapsulated within a cationic liposome (DOTAP: DOPE at 1:1 molar ratio). Also included in the complex is a recombinant anti-transferrin receptor single chain antibody fragment, which serves to target the complex to tumor cells (both primary and metastatic). For extended stability and shelf life the complex, in the presence of 10% sucrose, is lyophilized and stored at 4°C for up to six months. Mutation of p53 is one of the most common abnormalities in human cancer and is associated with poor prognosis. Replacement of functional p53 should restore both cell cycle control and apoptosis leading to increased efficacy of conventional therapies.

In vitro pre-clinical studies have shown that this complex has a high transfection efficiency (even after lyophilization and storage) in tumor cells of various types including prostate, breast, head and neck, and pancreas; but not in normal fibroblast cells. More significantly, based upon histological detection of X-gal expression, the exogenous gene was evident only in the tumors, and not in the normal tissues or organs such as the lung, liver, bone marrow or large intestine, after intravenous administration of the complex into mice bearing human tumor xenografts. In pre-clinical efficacy experiments, significant tumor growth inhibition was evident after treatment with the combination of systemically delivered complex plus standard radiation or chemotherapy. Throughout these efficacy studies the weights of the animals were monitored as an indication of toxicity. There was no significant weight loss or animal deaths attributable to the complex. Thus, these complexes do not appear to have major toxicity issues.

We propose to perform a Phase I clinical trial of the complex carrying wtp53 to determine safety, maximum tolerated dose and/or optimal biological dose, and anti-tumor activity. (The Phase I trial of complex with wtp53 will be performed at the Lombardi Cancer Center of Georgetown University, Washington D.C.)

